Journal of Neurotrauma 2018 vol.35 N18, pages 2145-2158

Non-invasive activation of cervical spinal networks after severe paralysis

Gad P., Lee S., Terrafranca N., Zhong H., Turner A., Gerasimenko Y., Edgerton V.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© Copyright 2018, Mary Ann Liebert, Inc. 2018. Paralysis of the upper extremities following cervical spinal cord injury (SCI) significantly impairs one's ability to live independently. While regaining hand function or grasping ability is considered one of the most desired functions in tetraplegics, limited therapeutic development in this direction has been demonstrated to date in humans with a high severe cervical injury. The underlying hypothesis is that after severe cervical SCI, nonfunctional sensory-motor networks within the cervical spinal cord can be transcutaneously neuromodulated to physiological states that enable and amplify voluntary control of the hand. Improved voluntary hand function occurred within a single session in every subject tested. After eight sessions of non-invasive transcutaneous stimulation, combined with training over 4 weeks, maximum voluntary hand grip forces increased by ~325% (in the presence of stimulation) and ~225% (when grip strength was tested without simultaneous stimulation) in chronic cervical SCI subjects (American Spinal Injury Association Impairment Scale [AIS] B, n = 3; AIS C, n = 5) 1-21 years post-injury). Maximum grip strength improved in both the left and right hands and the magnitude of increase was independent of hand dominance. We refer to the neuromodulatory method used as transcutaneous enabling motor control to emphasize that the stimulation parameters used are designed to avoid directly inducing muscular contractions, but to enable task performance according to the subject's voluntary intent. In some subjects, there were improvements in autonomic function, lower extremity motor function, and sensation below the level of the lesion. Although a neuromodulation-training effect was observed in every subject tested, further controlled and blinded studies are needed to determine the responsiveness of a larger and broader population of subjects varying in the type, severity, and years post-injury. It appears rather convincing, however, that a "central pattern generation" phenomenon as generally perceived in the lumbosacral networks in controlling stepping neuromodulator is not a critical element of spinal neuromodulation to regain function among spinal networks.

http://dx.doi.org/10.1089/neu.2017.5461

Keywords

cervical spinal cord injury, non-invasive spinal cord stimulation, tetraplegia, upper extremity rehabilitation

References

[1] Ethier, C. and Miller, L.E. (2015). Brain-controlled muscle stimulation for the restoration of motor function. Neurobiol. Dis. 83, 180-190

[2] Bensmaia, S.J. and Miller, L.E. (2014). Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. Nature Rev. Neurosci. 15, 313-325

[3] Lu, D.C., Edgerton, V.R., Modaber, M., AuYong, N., Morikawa, E., Zdunowski, S., Sarino, M.E., Sarrafzadeh, M., Nuwer, M.R., Roy, R.R. and Gerasimenko, Y. (2016). Engaging Cervical Spinal Cord Networks to Reenable Volitional Control of Hand Function in Tetraplegic Patients. Neurorehabil. Neural Repair 30, 951-962

[4] Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., Ferreira, C., Willhite, A., Rejc, E., Grossman, R.G., and Edgerton, V.R. (2011). Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet 377, 1938-1947

[5] Rejc, E., Angeli, C., and Harkema, S. (2015). Effects of Lumbosacral Spinal Cord Epidural Stimulation for Standing after Chronic Complete Paralysis in Humans. PloS One 10, e0133998

[6] Grahn, P.J., Lavrov, I.A., Sayenko, D.G., Van Straaten, M.G., Gill, M.L., Strommen, J.A., Calvert, J.S., Drubach, D.I., Beck, L.A., Linde, M.B., Thoreson, A.R., Lopez, C., Mendez, A.A., Gad, P.N., Gerasimenko, Y.P., Edgerton, V.R., Zhao, K.D., and Lee, K.H. (2017). Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. Mayo Clin. Proc. 92, 544-554

[7] Gerasimenko, Y.P., Lu, D.C., Modaber, M., Zdunowski, S., Gad, P., Sayenko, D.G., Morikawa, E., Haakana, P., Ferguson, A.R., Roy, R.R., and Edgerton, V.R. (2015). Noninvasive reactivation of motor descending control after paralysis. J. Neurotrauma 32, 1968-1980

[8] Gerasimenko, Y., Gad, P., Sayenko, D., McKinney, Z., Gorodnichev, R., Puhov, A., Moshonkina, T., Savochin, A., Selionov, V., Shigueva, T., Tomilovskaya, E., Kozlovskaya, I., and Edgerton, V.R. (2016). Integration of sensory, spinal, and volitional descending inputs in regulation of human locomotion. J. Neurophysiol. 116, 98-105

[9] Hoffman, H., Sierro, T., Niu, T., Sarino, M.E., Sarrafzadeh, M., McArthur, D., Edgerton, V.R., and Lu, D.C. (2017). Rehabilitation of hand function after spinal cord injury using a novel handgrip device: a pilot study. J. Neuroeng. Rehabil. 14, 22

[10] Gerasimenko, Y., Gorodnichev, R., Puhov, A., Moshonkina, T., Savochin, A., Selionov, V., Roy, R.R., Lu, D.C., and Edgerton, V.R. (2015). Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. J. Neurophysiol. 113, 834-842

[11] Shah, P.K., Sureddi, S., Alam, M., Zhong, H., Roy, R.R., Edgerton, V.R., and Gerasimenko, Y. (2016). Unique spatiotemporal neuromodulation of the lumbosacral circuitry shapes locomotor success after spinal cord injury. J. Neurotrauma 33, 1709-1723

[12] Shah, P.K. and Gerasimenko, Y. (2016). Multi-site spinal stimulation strategies to enhance locomotion after paralysis. Neural Regen. Res. 11, 1926-1927

[13] Charissou, C., Amarantini, D., Baures, R., Berton, E., and Vigouroux, L. (2017). Effects of hand configuration on muscle force coordination, co-contraction and concomitant intermuscular coupling during maximal isometric flexion of the fingers. Eur. J. Applied Physiol. 117, 2309-2320

[14] Hubscher, C.H., Herrity, A.N., Williams, C.S., Montgomery, L.R., Willhite, A.M., Angeli, C.A., and Harkema, S.J. (2018). Improvements in bladder, bowel and sexual outcomes following task-specific locomotor training in human spinal cord injury. PloS One 13, e0190998

[15] Angeli, C.A., Edgerton, V.R., Gerasimenko, Y.P., and Harkema, S.J. (2014). Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain 137, 1394-1409

[16] Rejc, E., Angeli, C.A., Atkinson, D., and Harkema, S.J. (2017). Motor recovery after activity-based training with spinal cord epidural stimulation in a chronic motor complete paraplegic. Sci. Rep. 7, 13476

[17] House, J.H., Gwathmey, F.W., and Lundsgaard, D.K. (1976). Restoration of strong grasp and lateral pinch in tetraplegia due to cervical spinal cord injury. J. Hand Surg. 1, 152-159

[18] Carroll, S., Cooper, C., Brown, D., Sormann, G., Flood, S., and Denison, M. (2000). Australian experience with the Freehand System for restoring grasp in quadriplegia. Aust. N. Z. J. Surg. 70, 563-568

[19] Prochazka, A., Gauthier, M., Wieler, M., and Kenwell, Z. (1997). The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. Arch. phys.med. rehabil. 78, 608-614

[20] Ievins, A. and Moritz, C.T. (2017). Therapeutic stimulation for restoration of function after spinal cord injury. Physiology 32, 391-398

[21] Phillips, A.A., Squair, J.W., Sayenko, D.G., Edgerton, V.R., Gerasimenko, Y., and Krassioukov, A.V. (2017). An autonomic neuroprosthesis: noninvasive electrical spinal cord stimulation restores autonomic cardiovascular function in individuals with spinal cord injury. J. Neurotrauma 35, 446-451

[22] West, C.R., Phillips, A.A., Squair, J.W., Williams, A.M., Walter, M., Lam, T., and Krassioukov, A.V. (2018). Association of epidural stimulation with cardiovascular function in an individual with spinal cord injury. JAMA Neurol. 2018 Feb 19; Epub ahead of print

[23] Gad, P.N., Roy, R.R., Zhong, H., Lu, D.C., Gerasimenko, Y.P., and Edgerton, V.R. (2014). Initiation of bladder voiding with epidural stimulation in paralyzed, step trained rats. PloS One 9, e108184

[24] Gad, P.N., Roy, R.R., Zhong, H., Gerasimenko, Y.P., Taccola, G., and Edgerton, V.R. (2016). Neuromodulation of the neural circuits controlling the lower urinary tract. Exp. Neurol. 285, 182-189

[25] Herman, R., He, J., D'Luzansky, S., Willis, W., and Dilli, S. (2002). Spinal cord stimulation facilitates functional walking in a chronic, incomplete spinal cord injured. Spinal Cord 40, 65-68

[26] Gerasimenko, Y.P., Lu, D.C., Modaber, M., Zdunowski, S., Gad, P., Sayenko, D.G., Morikawa, E., Haakana, P., Ferguson, A.R., Roy, R.R., and Edgerton, V.R. (2015). Noninvasive reactivation of motor descending control after paralysis. J. Neurotrauma 32, 1968-1980

[27] Gad, P., Gerasimenko, Y., Zdunowski, S., Turner, A., Sayenko, D., Lu, D.C., and Edgerton, V.R. (2017). Weight bearing over-ground stepping in an exoskeleton with non-invasive spinal cord neuromodulation after motor complete paraplegia. Front. Neurosci. 11, 333

[28] Sunshine, M.D., Cho, F.S., Lockwood, D.R., Fechko, A.S., Kasten, M.R., and Moritz, C.T. (2013). Cervical intraspinal microstimulation evokes robust forelimb movements before and after injury. J. Neural Eng. 10, 036001

[29] Iwahara, T., Atsuta, Y., Garcia-Rill, E., and Skinner, R.D. (1992). Spinal cord stimulation-induced locomotion in the adult cat. Brain Res. Bull. 28, 99-105

[30] Beaumont, E., Onifer, S.M., Reed, W.R., and Magnuson, D.S. (2006). Magnetically evoked inter-enlargement response: an assessment of ascending propriospinal fibers following spinal cord injury. Exp. Neurol. 201, 428-440

[31] Shah, P.K., Garcia-Alias, G., Choe, J., Gad, P., Gerasimenko, Y., Tillakaratne, N., Zhong, H., Roy, R.R., and Edgerton, V.R. (2013). Use of quadrupedal step training to re-engage spinal interneuronal networks and improve locomotor function after spinal cord injury. Brain 136, 3362-3377

[32] Courtine, G., Song, B., Roy, R.R., Zhong, H., Herrmann, J.E., Ao, Y., Qi, J., Edgerton, V.R., and Sofroniew, M.V. (2008). Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. Nat. Med. 14, 69-74

[33] Gerasimenko, Y., Musienko, P., Bogacheva, I., Moshonkina, T., Savochin, A., Lavrov, I., Roy, R.R., and Edgerton, V.R. (2009). Propriospinal bypass of the serotonergic system that can facilitate stepping. J. Neurosci. 29, 5681-5689

[34] Bareyre, F.M., Kerschensteiner, M., Raineteau, O., Mettenleiter, T.C., Weinmann, O., and Schwab, M.E. (2004). The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. Nat. Neurosci. 7, 269-277

[35] Houle, J.D., Tom, V.J., Mayes, D., Wagoner, G., Phillips, N., and Silver, J. (2006). Combining an autologous peripheral nervous system ''bridge'' and matrix modification by chondroitinase allows robust, functional regeneration beyond a hemisection lesion of the adult rat spinal cord. J. Neurosci. 26, 7405-7415

[36] Peckham, P.H., Keith, M.W., Kilgore, K.L., Grill, J.H., Wuolle, K.S., Thrope, G.B., Gorman, P., Hobby, J., Mulcahey, M.J., Carroll, S., Hentz, V.R., and Wiegner, A; Implantable Neuroprosthesis Research Group. (2001). Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. Arch. Phys. Med. Rehabil. 82, 1380-1388

[37] Gad, P., Choe, J., Shah, P., Garcia-Alias, G., Rath, M., Gerasimenko, Y., Zhong, H., Roy, R.R., and Edgerton, V.R. (2013). Sub-threshold spinal cord stimulation facilitates spontaneous motor activity in spinal rats. J. Neuroeng. Rehabil. 10, 108

[38] Gerasimenko, Y., Sayenko, D., Gad, P., Liu, C.T., Tillakaratne, N.J., Roy, R.R., Kozlovskaya, I., and Edgerton, V.R. (2016). Feedforwardness of spinal networks in posture and locomotion. Neuroscientist 2016 Dec 1; Epub ahead of print